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Analgesic drug use in patients with coronary artery disease

Stosowanie leków przeciwbólowych u pacjentów z chorobą niedokrwienną serca

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Abstract

Introduction. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the management of pain in a variety of conditions. Available data clearly indicate, that the use of NSAIDs is associated with a number of adverse effects, especially in patients with cardiovascular disease. The aim of the study was to assess the prevalence and frequency of analgesic drug use in patients with coronary heart disease and knowledge about possible interactions of these drugs with conventional cardiac therapy.

Material and methods. The study included 183 patients with ischaemic heart disease, hospitalised in the tertiary cardiological centre. Data on the use of analgesics and patients' knowledge about their safety were collected using self-prepared questionnaire. Information about current medication, accompanying diseases and blood-test results were checked in patients' medical records.

Results. In the examined group, regular use of analgesic drugs (defined as at least three times per week) was reported by 29 subjects (15.8%). The most frequently used analgesics were NSAIDs and paracetamol, with their regular use reported by 7.0% and 8.8% of the respondents respectively. The majority of patients using NSAIDs were not aware about their possible interactions with antiplatelet therapy and did not consult the use of analgesics with a physician. Only 19.8% of patients admitted, that they received the information about analgesics from their doctor.

Conclusions. The regular use of analgesic drugs by 15.8% of patients with coronary artery disease is a significant concern. Patients with coronary heart disease should be provided with detailed information and recommendations about safe analgesic therapy and alternatives for NSAIDs.

Key words: coronary artery disease, analgesics, NSAIDs, cardiovascular risk

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Introduction

Non-opioid analgesic drugs, namely non-steroidal anti-inflammatory drugs (NSAIDs) and few drugs without significant anti-inflammatory action (paracetamol [*acetaminophen*], metamizole) are commonly used by patients in treatment of acute and chronic pain. Chronic pain can affect even 20.0% of the adult European population and its frequency increases with age and comorbidities [1]. NSAIDs are among the most widely used and prescribed

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therapeutic agents, as they bring relief to a wide range of pain. Nevertheless, the efficiency of NSAIDs is limited by their potentially serious adverse effects. For many years, gastrointestinal bleeding was considered the main worry in relation to NSAID use. Recently, the cardiovascular safety of NSAIDs use has become a concern. Nowadays, it is widely accepted that all non-aspirin NSAIDs not only increase the risk of bleeding, but also increase a risk of thrombotic complications [2]. There are known drug-to-drug interactions of NSAIDs with some antihypertensives, diuretics and antithrombotic drugs. NSAIDs may compromise the cardioprotective effect of aspirin, competitively binding to COX-1 and interfering with the mechanism of antiplatelet activity [3].

Even short term administration of NSAIDs in patients after myocardial infarction was proven to increase significantly the risk of bleeding, recurrent myocardial infarction, stroke and cardiovascular death [4].

Data about the cardiovascular safety of paracetamol and metamizole are sparse, however they are generally considered safe [5, 6].

Current guidelines discourage the use of NSAIDs in patients with coronary heart disease [7], but as those drugs are available over-the-counter, the real exposure of high-risk patients to these agents is difficult to evaluate. There is no data on the real-life scale of the problem of analgesic therapy in patients with coronary heart disease in the Polish population.

The purpose of this study was to analyse the prevalence, frequency and type of analgesic drugs used among patients with coronary artery disease. Additionally, we sought to assess the patients knowledge about possible interactions between analgesic drugs and conventional cardiac therapy.

Material and methods

The study was conducted among patients with coronary artery disease, hospitalised in the tertiary cardiology centre between October 2015 and July 2016. The main inclusion criterion was the diagnosis of coronary artery disease at the admission to the cardiological ward. The study included both — patients with stable angina being admitted electively to hospital to undergo scheduled coronary angiography and patients with acute coronary syndromes. The exclusion criteria were inability to communicate, cognitive dysfunction and lack of consent.

Information about the use of analgesics were collected by face-to-face interviews using the self-prepared survey questionnaires. Questionnaires were distributed and collected by students from the Students' Scientific Group at the Clinic. The questionnaire contained 16 closed- and open-ended questions. The first part comprised of the patient's personal and demographic data, past medical history, comorbidities, habits and medication used. The second part referred to the use of analgesic drugs by the patient in the last year and contained questions about the type of analgesic drug, frequency of its use, reasons for analgesic treatment, sources of information about analgesics, and questions about the communication with physician regarding the use of pain relieving drugs (did the patient consult the use of these drugs with a physician, if the patient received information about side effects of the drugs from a physician). For each type of analgesic listed, the patients were asked about the frequency of its use — the answers varied from never to more than once per day. Based on the reported frequency, the respondents were divided into two groups — regular users and non-regular/ /non-users. Regular analgesic drugs use was defined as taking them at least three times per week.

The questionnaire also analysed the patient's awareness of possible interactions of analgesics with conventional cardiac treatment and knowledge of safety of NSAIDs use for patients after cardiovascular events.

Information about laboratory tests and medication used during current hospitalisation were extracted from patients medical records. The study protocol was approved by the local ethics committee.

Statistical analysis

Statistica 12.0 software was used for data management and statistical analysis (StatSoft, Statistica 12.0, Tulsa, Oklahoma, USA). The chi-squared test was used to evaluate the comparisons of qualitative data, whereas t-student tests for quantitative data. For all the tests, the p value <0.05 was considered statistically significant. Quantitative data is expressed as mean values and standard deviations while qualitative variables as number and percent values.

Results

The study group included 183 patients, 55 women (30.1%) and 128 men (69.9%). The mean age of the study population was 68.7 ± 10.7 years. Seventy nine patients (43.2%) were hospitalised because of acute coronary syndrome and — 104 (56.8%) were admitted for elective coronary angiography. The majority of patients from the study group had hypertension (n = 141, 77.0%). Diabetes mellitus was present in 64 (35.0%) and hypercholesterolaemia in 109 (59.7%) subjects. There were 28 current smokers (15.3%) and 86 ex-smokers (47.0%) in the population under the study. Ninety-four patients (51.4%) included in the study had a history of previous myocardial infarction and 21 (11.4%) a history of stroke. The majority of patients (n = 121; 66.1%) underwent the percutaneous coronary intervention in the past. Diagnosis of atrial fibrillation (in the history or during current hospitalisation) was established in 75 patients (41.0%).

Table 1. Clinical characteristics of the study group with reference to the regular analgesic drug use. The data is expressed as mean values ± standard deviations (SD) for continuous variables or number and percent for categorical variables

	Regular analgesic drug user N = 29	Non-users/non-regular analgesic drug user N = 154	p*
Age (years)	70.4 ± 11.5	68.4 ± 10.6	0.37
Female n (%)	13 (44.8%)	42 (27.3%)	**0.05**
Hypertension n (%)	23 (79.3%)	118 (76.6%)	0.48
Diabetes mellitus n (%)	13 (44.8%)	51 (33.1%)	0.15
Hyperlipidaemia n (%)	13 (44.8%)	61 (39.6%)	0.37
Smoking n (%)	3 (10.3%)	25 (16.2%)	0.31
Urgent admission to hospital n (%)	12 (41.3%)	67 (43.5%)	0.61
Previous myocardial infarction n (%)	13 (44.8%)	81 (52.6%)	0.28
Previous stroke n (%)	6 (20.7%)	15 (9.7%)	0.08
BMI (kg/m^2)	28.5 ± 6.3	28.3 ± 5.6	0.91
Serum creatinine (µmol/l)	98.3 ± 38.2	98.4 ± 61.2	0.99
Serum glucose (mmol/l)	7.3 ± 3.1	6.4 ± 2.3	0.09
Total cholesterol (mmol/l)	4.4 ± 1.3	4.2 ± 1.2	0.40
LDL-cholesterol (mmol/l)	2.4 ± 1.1	2.3 ± 1.1	0.67
HDL-cholesterol (mmol/l)	1.3 ± 0.4	1.2 ± 0.4	0.27
Triglicerides (mmol/l)	1.4 ± 0.6	1.4 ± 0.7	0.67

*p value calculated with t-Student test for independent variables (continuous variables) and Chi-square (categorical variables); BMI – body mass index

The majority of the examined patients (n = 116; 63.4%) were retired. Forty participants (21.9%) declared higher education.

In the examined group, 116 (63.4%) patients declared the use of analgesic drugs over the last year. Fifty patients (27.3%) declared the use of more than one type of analgesics. The regular use of analgesics (defined as at least three times per week) was reported by 29 patients (15.8%) of the examined group.

There were no differences in age and cardiovascular risk factor profile between the regular analgesics users and the rest of the group. Regular use of analgesics was reported more commonly by women than men. Results are summarised in Table 1.

In the group of patients taking analgesics regularly, non-steroidal anti-inflammatory drugs and paracetamol were the most commonly administered medications (Table 2). Sixteen patients (8.7%) reported the regular use of paracetamol and 13 (7.0%) declared the regular use of NSAIDs. Among NSAIDs, ibuprofen was the most frequently used in the examined group. Regular NSAIDs users did not differ from analgesic drug non-users in refer to age, gender and burden of cardiovascular risk factors.

The main reasons for using analgesic drugs were: musculoskeletal pain (n = 58), headache (n = 49) and arthralgia (n = 35). About half of those patients, who reported the use of analgesic in the last year (n = 56) declared, that they had received the information about analgesics from family, acquaintances and advertising on TV. Only 44.0% (n = 51) of patients taking analgesic drugs consulted it with their physicians. The majority of subjects using analgesics (n = 93; 80.2%) did not receive any information about drug-to-drug interactions and side effects of these medications. Only 38 patients (20.8%) were able to answer correctly

Table 2. Analgesic drugs use reported by patients with ischaemic heart disease (irrespective of the frequency of use). Some patients used more than one drug and therefore the number of patients and percentages do not add up to 183 and 100 respectively

Drug	Number of patients, n (%)
NSAIDs	107 (58.5%)
ibuprofen	39 (21.3%)
aspirin (acetylsalicylic acid)	27 (14.7%)
ketoprofen	19 (10.3%)
diclofenac	15 (8.2%)
nimesulid	4 (2.2%)
meloxicam	3 (1.6%)
naproxen	1 (0.5%)
paracetamol	66 (36.0%)
metamizole	9 (4.9%)
tramadol	6 (3.3%)

for question about possible interactions of analgesics with antiplatelet drugs. Twelve patients (13.9%) believed that using analgesics has no influence on antiplatelet therapy. Most analgesic drug users did not know if these drugs can interfere with antiplatelet medication (n = 133; 72.7%). Similarly, the patients were not aware of possible interactions of analgesics with antihypertensive therapy (answer "yes" was given only by 39 respondents and "do not know" by 116 patients, 28 participants reported that there are no interactions between analgesics and antihypertensive medication). Seventy-five respondents (41.0%) reported concerns about safety of analgesics in patients after myocardial infarction, while 25 (13.7%) believed that analgesic use after myocardial infarction is safe.

Discussion

The study demonstrated that the use of analgesic drugs by patients with coronary artery disease is frequent, reported by 63.4% (n = 116) of participants. In our study almost 16% of participants declared the regular use of analgesic drugs, defined as at least three times a week. As our study was conducted in selected population of high-risk patients with established coronary heart disease, it makes it difficult to compare the results directly with those coming from general population.

Nonetheless, the wide use of analgesics in the past year was also documented in previous large studies conducted in general population, investigating the same time period. Wilcox et al. showed, that among 9083 general population respondents, 83.0% of individuals reported over-the-counter analgesics use in the past year, and 37.0% of those, reported using them daily or several times a week [8]. In the Dutch study examining the frequency of over-the-counter NSAIDs use in general population, the high-risk sample was separately analysed, revealing that regular use of NSAIDs was reported by 13.0% of high-risk participants [9]. The prospective study undertaken in myocardial infarction survivors, proved that at least one prescription claim for NSAIDs treatment after discharge was identified for 33.8% of patients [4]. This Danish study documented, that even short administration of NSAIDs resulted in significant increase of both bleeding risk and risk of thrombotic events . There was no safe therapeutic window for NSAIDs co-administration, because even short--term (0–3 days) treatment was related with the increased risk. Similar results come from recently published meta-analysis, based on the data of 446 763 individuals, showing that NSAIDs use is associated with increased risk of myocardial infarction [10].

In our study, regular NSAIDs use was reported by 7.0% of participants, but taking into account the absolute number of patients with coronary heart disease it remains a significant concern. In Poland in 2014 the total number of percutaneous coronary procedures performed was 126 241 [11], which in the context of our results (7.0% regular NSAIDs users) may translate into over 8800 subjects yearly exposed to potentially harmful analgesic therapy.

Precise summary information on cardiovascular risk with NSAIDs has been available since 2006 and current guidelines of the European Society of Cardiology discourage the use of non-aspirin NSAIDs in patients with established or at high risk of cardiovascular disease [7]. Pain treatment should begin with paracetamol and optimisation of treatment of underlying disease, then weak opioids use may be considered. If initial therapy is insufficient, it is reasonable to use nonselective NSAIDs such as naproxen [12]. Evidence suggests that there are significant differences between commonly used members of the NSAIDs class [13]. In our study, the most popular NSAIDs were ibuprofen, ketoprofen and diclofenac. Naproxen, which still appears to have the least harmful cardiovascular risk profile, also in patients with myocardial infarction and heart failure, was used only by one subject.

Nevertheless, even when analgesic therapy was prescribed by a doctor, the patients did not receive adequate information and NSAIDs were perceived as safe drugs without significant interaction with co-administered cardiovascular medication. Low awareness about the adverse effects of NSAIDs was also documented in other studies [14, 15].

On the other hand, in the examined population, the regular use of paracetamol was reported with equal frequency to the regular use of NSAIDs. The cross-sectional character of our study does not allow for interpretation of the time-trends and proportions between NSAIDs and paracetamol use in the last decade, but it cannot be excluded, that although general awareness of analgesic safety is unsatisfactory, paracetamol was chosen as a safer alternative for pain therapy.

Paracetamol has been considered as safe and relatively effective for some forms of minor pain. The influence of paracetamol on cardiovascular events was examined only in a few studies, some of them linked paracetamol use with blood pressure elevation, hypertension development and myocardial infarction incidence [6]. Recent retrospective analysis confirmed the cardiovascular safety of paracetamol in 10878 exposed subjects followed by ten years [16], supporting the choice of paracetamol therapy for pain in patients presenting with cardiovascular risk factors.

In our study, the female gender was associated with regular analgesic drug use. Similar observations were reported by others. In the Norwegian population, the use of over--the-counter analgesics was related to the female gender, physical inactivity and chronic pain [17]. Data from NHANES survey also indicated, that women were more likely to use NSAIDs regularly [18]. Higher prevalence of analgesics use in women compared to men is probably related to gender

differences in pain perception, efficacy of pain medication and prevalence of chronic non-malignant pain [19].

We were not able to identify other factors related with regular analgesic drug use. The group of regular analgesic drug-users did not differ with regard to age and comorbidities from the rest of the interviewed patients. Previous, larger population-based studies identified poor self-rated health, increasing age, obesity and smoking as factors related with continuous regular analgesic use [20]. Relatively narrow age range and limited number of participants, as well as homogeneous population of high cardiovascular risk patients under the study may be responsible for this discrepancy in the obtained results.

Identification of regular analgesic drug users characteristics is important, as understanding who is likely to use NSAIDs enables more targeted messaging.

Based on our results, it is clear that there is a need to improve patients knowledge about potential interactions of analgesic drugs with standard antianginal therapy.

Thus, we suggest that in patients with established coronary heart disease and especially those undergoing interventional therapies requiring subsequent dual antiplatelet therapy or combined antiplatelet and anticoagulant therapy, detailed history regarding the use of analgesic drugs should be taken and clear instructions about safe pain therapy should be provided.

There are several limitations of our study. The study was based on questionnaires, and the structure of the method itself may bias the results. Fixed-choice questionnaires force the respondent to answer questions that he or she may be ignorant or have different understanding based on personal perception. Face-to-face survey and direct administration of the questionnaire in our study should improve the quality of data collected and minimise the errors related to difficulties in understanding the complex questions.

The study sample is relatively small, but its characteristics reflects the typical profile of patients with coronary heart disease. Our study, conducted among subjects hospitalised to undergo coronary artery intervention, illustrates real-life prevalence of regular analgesics drug use. Although we were not able to clearly define the coexisting diseases requiring analgesics, we have proven, that pain treatment remains problematic and needs appropriate caution and attention.

Conclusions

The regular use of analgesic drugs by 15.8% of patients with coronary artery disease is a significant concern. Women are more likely than men to be regular analgesic drugs users. Patients with coronary heart disease should be provided with detailed information and recommendations about safe analgesic therapy and alternatives for NSAIDs.

Conflict of interests

None declared.

Streszczenie

Wstęp. Niesteroidowe leki przeciwzapalne (NLPZ) są powszechnie używane do uśmierzania bólu w przebiegu różnorodnych schorzeń. Dostępne dane jasno wskazują, że stosowanie NLPZ jest związane ze znaczną liczbą efektów ubocznych, zwłaszcza wśród pacjentów z chorobą sercowo-naczyniową. Celem pracy było określenie częstości stosowania leków przeciwbólowych wśród pacjentów z chorobą niedokrwienną serca oraz wiedzy pacjentów na temat potencjalnych interakcji tych leków ze standardowym leczeniem kardiologicznym.

Materiał i metody. Badanie przeprowadzono wśród 183 pacjentów z chorobą niedokrwienną serca hospitalizowanych w referencyjnym ośrodku kardiologicznym. Dane na temat stosowania leków przeciwbólowych oraz wiedzy pacjentów o ich bezpieczeństwie były pozyskiwane z użyciem kwestionariusza. Informacje na temat przyjmowanych leków, współistniejących chorób oraz badań laboratoryjnych zostały uzyskane z historii chorób pacjentów.

Wyniki. Regularne stosowanie leków przeciwbólowych (co najmniej trzykrotne w ciągu tygodnia) zadeklarowało 29 pacjentów (15,8%). Najczęściej stosowanymi lekami przeciwbólowymi były NLPZ oraz paracetamol, których regularne stosowanie podało 7% i 8,8% osób. Większość pacjentów stosujących NLPZ nie było świadomych potencjalnych interakcji tych leków z terapią przeciwpłytkową i nie konsultowało stosowania leków przeciwbólowych z lekarzem. Zaledwie 19,8% pacjentów przyznało, że otrzymało informację na temat leków przeciwbólowych od lekarza.

Wnioski. Regularne stosowanie leków przeciwbólowych przez 15,8% pacjentów z chorobą wieńcową serca stanowi istotny problem. Pacjenci z chorobą wieńcową serca powinni otrzymywać dokładne informacje oraz zalecenia na temat bezpiecznej terapii przeciwbólowej oraz alternatywy dla NLPZ.

Słowa kluczowe: choroba wieńcowa serca, leki przeciwbólowe, NLPZ, ryzyko sercowo-naczyniowe

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References

1. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. Br J Anaesth. 2013; 111(1): 13–18, doi: 10.1093/bja/aet123, indexed in Pubmed: 23794640.
2. Baigent C, Bhala N, Emberson J, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. The Lancet. 2013; 382(9894): 769–779, doi: 10.1016/s0140-6736(13)60900-9.
3. Nalamachu S, Pergolizzi J, Raffa R, et al. Drug-drug interaction between NSAIDS and low-dose aspirin: a focus on cardiovascular and GI toxicity. Expert Opin Drug Saf. 2014; 13(7): 903–917, doi: 10.1517/14740338.2014.924924.
4. Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA. 2015; 313(8): 805–814, doi: 10.1001/jama.2015.0809, indexed in Pubmed: 25710657.
5. Andrade S, Bartels DB, Lange R, et al. Safety of metamizole: a systematic review of the literature. J Clin Pharm Ther. 2016; 41(5): 459–477, doi: 10.1111/jcpt.12422, indexed in Pubmed: 27422768.
6. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006; 113(12): 1578–1587, doi: 10.1161/CIRCULATIONAHA.105.595793, indexed in Pubmed: 16534006.
7. Roffi M, Patrono C, Collet JP, et al. Authors, ESC Scientific Document Group. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37(3): 267–315, doi: 10.1093/eurheartj/ehv320, indexed in Pubmed: 26320110.
8. Wilcox CM, Cryer B, Triadafilopoulos G. Patterns of use and public perception of over-the-counter pain relievers: focus on nonsteroidal antiinflammatory drugs. J Rheumatol. 2005; 32(11): 2218–2224, indexed in Pubmed: 16265706.
9. Koffeman AR, Valkhoff VE, Celik S, et al. High-risk use of over-the-counter non-steroidal anti-inflammatory drugs: a population-based cross-sectional study. Br J Gen Pract. 2014; 64(621): e191–e198, doi: 10.3399/bjgp14X677815, indexed in Pubmed: 24686883.
10. Bally M, Dendukuri N, Rich B, et al. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ. 2017; 357: j1909, indexed in Pubmed: 28487435.
11. Ochała A, Siudak Z, Legutko J, et al. Percutaneous interventions in cardiology in Poland in the year 2014. Summary report of the Association of Cardiovascular Interventions of the Polish Cardiac Society AISN PTK. Post Kardiol Interw. 2015; 11(3): 177–181, doi: 10.5114/pwki.2015.54009, indexed in Pubmed: 26677356.
12. Schmidt M, Lamberts M, Olsen AM, et al. Cardiovascular safety of non-aspirin non-steroidal anti-inflammatory drugs: review and position paper by the working group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J. 2016; 37(13): 1015–1023, doi: 10.1093/eurheartj/ehv505.
13. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ. 2011; 342(jan11 1): c7086–c7086, doi: 10.1136/bmj.c7086.
14. Karakitsiou M, Varga Z, Kriska M, et al. Risk perception of NSAIDs in hospitalized patients in Greece. Bratisl Lek Listy. 2017; 118(7): 427–430, doi: 10.4149/BLL_2017_083, indexed in Pubmed: 28766354.
15. Varga Z, Kriška M, Kristová V, et al. Analysis of non-steroidal anti-inflammatory drug use in hospitalized patients and perception of their risk. Interdiscip Toxicol. 2013; 6(3): 141–144, doi: 10.2478/intox-2013-0022, indexed in Pubmed: 24678251.
16. Fulton RL, Walters MR, Morton R, et al. Acetaminophen use and risk of myocardial infarction and stroke in a hypertensive cohort. Hypertension. 2015; 65(5): 1008–1014, doi: 10.1161/HYPERTENSIONAHA.114.04945, indexed in Pubmed: 25801870.
17. Dale O, Borchgrevink PC, Fredheim OM, et al. Prevalence of use of non-prescription analgesics in the Norwegian HUNT3 population: Impact of gender, age, exercise and prescription of opioids. BMC Public Health. 2015; 15: 461, doi: 10.1186/s12889-015-1774-6, indexed in Pubmed: 25934132.
18. Davis JS, Lee HY, Kim J, et al. Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. Open Heart. 2017; 4(1): e000550, doi: 10.1136/openhrt-2016-000550, indexed in Pubmed: 28674622.
19. Khan F, Ahmed A, Chawla T, et al. Effect of gender on pain perception and analgesic consumption in laparoscopic cholecystectomy: An observational study. J Anaesthesiol Clin Pharmacol. 2013; 29(3): 337, doi: 10.4103/0970-9185.117095.
20. Hargreave M, Andersen TV, Nielsen A, et al. Factors associated with a continuous regular analgesic use - a population-based study of more than 45,000 Danish women and men 18-45 years of age. Pharmacoepidemiol Drug Saf. 2010; 19(1): 65–74, doi: 10.1002/pds.1864, indexed in Pubmed: 19757417.